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EXAMINER	
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1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,336	JOLIVET ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15 and 17-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, filed 01/15/09, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Status of the Claims

Claims 1, 3-15, 17-60 are currently pending in this application and are the subject of the Office action.

REJECTIONS

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47 and 58 are rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Lokich et al. (Lokich et a. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record)

De Bono et al. disclose pharmacokinetic and pharmacodynamic results of troxacitabine in thirty-nine patients with **advanced solid malignancies** wherein said troxacitabine was given at eight dose levels ranging from 0.12 to 1.8 mg/m2/day via a 30-min intravenous infusion for five days (abstract). De Bono et al. teach that the pharmacokinetics of troxacitabine is dose-independent wherein the mean (SD) values for the volume of distribution at steady-state and clearance (Cl) were 60 (32 L and 161 (33) ml/min, respectively, on day 1. After treatment on the fifth day, terminal half-life values averaged 39 (63) hours, and Cl, was reduced by approximately 20%, averaging 127 (27) ml/min. The principal mode of drug elimination was renal. A patient with

metastatic ocular melanoma experienced a partial response. De Bono et al. further suggest that broad disease-directed evaluations of troxacitabine as a 30-minute infusion daily for 5 days every 4 weeks at a dose of 1.5 - 1.2 mg/m2/day, and possibly less frequent schedules, were warranted. De Bono et al. teach a method for treating patients with **solid malignancies**, including ocular melanoma, comprising administering an effective amount of troxacitabine via a 30-min intravenous infusion for a period of 120 hours (5 days) wherein a steady state plasma concentration of troxacitabine was achieved during the administration. De Bono et al. disclose that a patient with melanoma experienced a partial response is evidence that the dose range from 0.12 to 1.8 mg/m2/day via a 30-min intravenous infusion for five days is a therapeutically effective amount of troxacitabine.

However, De Bono et al. do not teach the instant claimed cancers, or continuous infusions for a period of at least 72 hours, or combination chemotherapy.

Lokich et al. teach that some anti-neoplastic agents are administered as a continuous 24-hours infusion for five or more days routinely, such as 5-fluorouracil and cladrabine, while some agents, for example, fludarabine and etoposide are administered as a daily bolus for three to five days. Lokich et al. teach that the **rationale for infusional administration for chemotherapeutic agents is generally based upon observing schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life following bolus administration would limit tumor cell exposure**; the infusion schedule may also mitigate the acute

and chronic toxicities commonly associated with high peak levels (page 15, col. 1, introduction section, lines 8-15; see also page 18, Table 3). Lokich et al. teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3). Lokich et al. also teach that the selection of a duration of infusion is often arbitrary or based on achieving specific objectives such as decreasing allergic, gastrointestinal or other adverse effects; the dose intensity (DI) and the maximum tolerated dose (MTD) for infusional schedules may be different from those achieved with bolus administration and as such may influence the clinical effectiveness of the therapy (page 15, col. 2, lines 3-10). Lokich et al. teach that for some agents, cumulative effects with infusional administration may result in accentuated toxicity necessitating adjustments in the dose rate in order to permit long term administration for weeks or even months (page 23, lines 3-8). Lokich et al. suggest that conceptually longer duration infusions permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction (page 23, col. 1, lines 8-18) and that the infusion schedule may also mitigate the acute and chronic toxicities commonly associated with high peak drug levels (page 15, col. 1, introduction section, lines 8-15; see also page 18, Table 3).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references to manipulate the period of the continuous infusion of troxacitabine as taught by De Bono et al. in view of the

teaching of Lokich et al. to optimize the therapeutic effects and minimize the drug-induced adverse effects associated with the infusion, including arriving at the instant claimed period of infusion. One would have been motivated to do so because Lokich et al suggest that conceptually longer duration infusions permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction (page 15, col. 1, introduction section, lines 8-15; page 23, col. 1, lines 8-18; see also MPEP 2144.05, II. B) and De Beno et al. disclose that bolus infusion of troxacitabine is associated with severe neutropenia. Besides, De Bono et al. disclose pharmacokinetic data that one of skill in the art could reasonably manipulate to arrive at the instant claimed dosing parameters with respect to duration of infusion, dosage amount, and steady state plasma concentration of troxacitabine since it is routine in the art to conduct pharmacokinetic studies of drugs that are intended to be use in humans.

Also, it would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references to treat any suitable cancer (e.g. pancreatic cancer) as taught by Chu et al. with troxacitabine via continuous intravenous infusion. One would have been motivated to do so because Chu et al. teach that various cell lines are sensitive to troxacitabine (e.g. pancreatic cancer; see Figure 4) and De Bono et al. teach that troxacitabine is useful in treating solid malignancies and both De Bono et al. and Lokich et al. are concerned with intravenous continuous infusion of chemotherapy.

Further, it would have been obvious to a person of skill in the art at the time the invention was made to combine troxacitabine with another conventionally known

chemotherapeutic drug for additive effect in treating a patient with cancer. One would have been motivated to do so because Chu et al. suggest that troxacitabine may be administered either alone, or in combination with other known anticancer or pharmaceutical agents, as well as in conjunction with other conventional cancer therapies, such as radiation treatment or surgery (col. 10, lines 50-59).

It is noted that Lokich et al. teach 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3), which overlaps with the instant claimed limitation "by continuous infusion for a period of at least 72 hours."

Regarding claim 47, De Bono et al. teach the identical instantly claimed troxacitabine for administration to a patient with advanced solid malignancies (= solid cancers) in a dose ranging from 0.12 to 1.8 mg/m2/day administered via a 30-min intravenous infusion for five days and the instant claim also recites solid malignancies (e.g. **pancreatic cancer**). Since the dose of troxacitabine as taught by De Bono et al. overlaps with the claimed dosage amount, one would reasonably expect that administration of the same drug to the same population in overlapping dosage amount via continuous infusion (e.g. over 96 hours) as encompassed by the prior art would also achieve similar steady state plasma concentration of troxacitabine, including the instant claimed plasma concentration of 0.03 to 2 μM. Hence, the term "wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0 μM is achieved during the administration," overlaps with the prior art.

With respect to the term "effective amount," De Bono et al. teach troxacitabine in a dosage amount that resulted in partial responses in patients with solid malignancies and therefore the dose of troxacitabine as taught by De Bono is an effective amount. Besides, said dose taught by De Bono overlaps with the dose disclosed by applicant of 0.7 to 12.5 mg/m2/day of troxacitabine (specification, page 14, lines 12-24).

With respect to the preamble, De Bono et al. teach a method of treating patients (= hosts) with solid malignancies (= tumor) comprising administering troxacitabine via a 30-minute continuous infusion to said hosts. Hence, the prior art encompasses a method for treating a patient with cancer.

With respect to claim 58, Lokich et al suggest continuous intravenous infusions as discussed above.

Claims 1, 3-15, 17-38, and 48-56, and 58-60 are rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Lokich et al. (Lokich et a. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record), in further view of Chu et al. (US Patent 5,817,667).

De Bono et al. disclose pharmacokinetic and pharmacodynamic results of troxacitabine in thirty-nine patients with **advanced solid malignancies** wherein said troxacitabine was given at eight dose levels ranging from 0.12 to 1.8 mg/m2/day via a 30-min intravenous infusion for five days (abstract). De Bono et al. teach that the

pharmacokinetics of troxacitabine is dose-independent wherein the mean (SD) values for the volume of distribution at steady-state and clearance (Cl) were 60 (32 L and 161 (33) ml/min, respectively, on day 1. After treatment on the fifth day, terminal half-life values averaged 39 (63) hours, and Cl, was reduced by approximately 20%, averaging 127 (27) ml/min. The principal mode of drug elimination was renal. A patient with **metastatic ocular melanoma** experienced a partial response. De Bono et al. further suggest that broad disease-directed evaluations of troxacitabine as a 30-minute infusion daily for 5 days every 4 weeks at a dose of 1.5 - 1.2 mg/m2/day, and possibly less frequent schedules, were warranted. De Bono et al. teach a method for treating patients with **solid malignancies**, including ocular melanoma, comprising administering an effective amount of troxacitabine via a 30-min intravenous infusion for a period of 120 hours (5 days) wherein a steady state plasma concentration of troxacitabine was achieved during the administration. De Bono et al. disclose that a patient with melanoma experienced a partial response is evidence that the dose range from 0.12 to 1.8 mg/m2/day via a 30-min intravenous infusion for five days is a therapeutically effective amount of troxacitabine.

However, De Bono et al. do not teach the instant claimed cancers, or continuous infusions for a period of at least 72 hours, or combination chemotherapy.

Lokich et al. teach that some anti-neoplastic agents are administered as a continuous 24-hours infusion for five or more days routinely, such as 5-fluorouracil and cladrabine, while some agents, for example, fludarabine and etoposide are

administered as a daily bolus for three to five days. Lokich et al. teach that the **rationale for infusional administration for chemotherapeutic agents is generally based upon observing schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life following bolus administration would limit tumor cell exposure**; the infusion schedule may also mitigate the acute and chronic toxicities commonly associated with high peak levels (page 15, col. 1, introduction section, lines 8-15; see also page 18, Table 3). Lokich et al. teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3). Lokich et al. also teach that the selection of a duration of infusion is often arbitrary or based on achieving specific objectives such as decreasing allergic, gastrointestinal or other adverse effects; the dose intensity (DI) and the maximum tolerated dose (MTD) for infusional schedules may be different from those achieved with bolus administration and as such may influence the clinical effectiveness of the therapy (page 15, col. 2, lines 3-10). Lokich et al. teach that for some agents, cumulative effects with infusional administration may result in accentuated toxicity necessitating adjustments in the dose rate in order to permit long term administration for weeks or even months (page 23, lines 3-8). Lokich et al. suggest that conceptually longer duration infusions permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction (page 23, col. 1, lines 8-18) and that the infusion schedule may also mitigate the acute and chronic toxicities commonly associated with

high peak drug levels (page 15, col. 1, introduction section, lines 8-15; see also page 18, Table 3).

Chu et al. (US Patent 5,817,667) teach a method for treatment of cancer in humans and other host animals comprising administering an effective amount of troxacitabine (column 3, lines 21-52). Chu et al. specifically teach that various **cancer cells lines are sensitive to troxacitabine, including leukemia, lymphoma, prostate, bladder, lung, colorectal, breast, pancreas, liver, ovarian cancers** (see Figure 4). Chu et al. teach that humans, equines, canines, bovines and other animals, and in particular, mammals, suffering from cancer can be treated by administering to the patient an **effective amount of (-)-OddC (i.e. troxacitabine)** or a pharmaceutically acceptable salt thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known anticancer or pharmaceutical agents; this treatment can also be administered in conjunction with other conventional cancer therapies, such as radiation treatment or surgery (col. 10, lines 50-59). Chu et al. also disclose that troxacitabine is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30mM, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient (cols. 10-11, Example 8, see especially col. 11, lines 13-19). Chu et al. teach alkylating agents (e.g. nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin); antimetabolites; nucleoside derivatives (e.g. 5-fluorouracil); nucleoside analog of dexocytidine (e.g. cytosine arabinoside); cytidine analog (e.g. 5-azacytidine); 2-fluoroadenoside-5'-

phosphate (Fludarabine); **anthracyclines**; hormonal agents ; natural products and their derivatives; 2-chlorodeoxyadenosine(col. 2, line 7 to col. 3, line 10). Chu et al. exemplify a method of treating leukemia in mice comprising administering L(-)-OddC twice daily for five days at a dose of 75 mg/kg (col.12,line 41 to col. 14, line 67, including Table 2). Chu et al. state that certain prostate cancer cell lines, leukemia cell lines, and colon cell lines show extreme sensitivity to (-)-OddC (col. 15, lines 4-7).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references to manipulate the period of the continuous infusion of troxacitabine as taught by De Bono et al. in view of the teaching of Lokich et al. to optimize the therapeutic effects and minimize the drug-induced adverse effects associated with the infusion, including arriving at the instant claimed period of infusion. One would have been motivated to do so because Lokich et al suggest that conceptually longer duration infusions permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction (page 15, col. 1, introduction section, lines 8-15; page 23, col. 1, lines 8-18; see also MPEP 2144.05, II. B) and De Beno et al. disclose that bolus infusion of troxacitabine is associated with severe neutropenia. Besides, De Bono et al. disclose pharmacokinetic data that one of skill in the art could reasonably manipulate to arrive at the instant claimed dosing parameters with respect to duration of infusion, dosage amount, and steady state plasma concentration of troxacitabine since it is routine in the art to conduct pharmacokinetic studies of drugs that are intended to be use in humans.

Also, it would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references to treat any suitable cancer (e.g. pancreatic cancer) as taught by Chu et al. with troxacitabine via continuous intravenous infusion. One would have been motivated to do so because Chu et al. teach that various cell lines are sensitive to troxacitabine (e.g. pancreatic cancer; see Figure 4) and De Bono et al. teach that troxacitabine is useful in treating solid malignancies and both De Bono et al. and Lokich et al. are concerned with intravenous continuous infusion of chemotherapy.

Further, it would have been obvious to a person of skill in the art at the time the invention was made to combine troxacitabine with another conventionally known chemotherapeutic drug for additive effect in treating a patient with cancer. One would have been motivated to do so because Chu et al. suggest that troxacitabine may be administered either alone, or in combination with other known anticancer or pharmaceutical agents, as well as in conjunction with other conventional cancer therapies, such as radiation treatment or surgery (col. 10, lines 50-59).

It is noted that Lokich et al. teach 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3), which overlaps with the instant claimed limitation "by continuous infusion for a period of at least 72 hours."

Regarding claim 1, De Bono et al. teach the identical instantly claimed troxacitabine for administration to a patient with advanced solid malignancies (= solid cancers) in a dose ranging from 0.12 to 1.8 mg/m2/day administered via a 30-min

intravenous infusion for five days and the instant claim also recites solid malignancies (e.g. **pancreatic cancer**). Since the dose of troxacitabine as taught by De Bono et al. overlaps with the claimed dosage amount, for example, claim 14, one would reasonably expect that administration of the same drug to the same population in overlapping dosage amount via continuous infusion (e.g. over 96 hours) as encompassed by the prior art would also achieve similar steady state plasma concentration of troxacitabine, including the instant claimed plasma concentration of 0.03 to 2 μM. Hence, the term "wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0 μM is achieved during the administration," overlaps with the prior art.

With respect to the term "effective amount," De Bono et al. teach troxacitabine in a dosage amount that resulted in partial responses in patients with solid malignancies and therefore the dose of troxacitabine as taught by De Bono is an effective amount. Besides, said dose taught by De Bono overlaps with the dose disclosed by applicant of 0.7 to 12.5 mg/m2/day of troxacitabine (specification, page 14, lines 12-24).

With respect to the term "wherein said cancer is lung cancer, prostate cancer, …, leukemia or lymphoma," Chu et al. teach that various cancer cells lines are sensitive to troxacitabine, including leukemia, lymphoma, prostate, bladder, lung, colorectal, breast, pancreas, liver, ovarian cancers (see Figure 4), which overlaps with the instant claimed limitation.

With respect to the preamble, the prior art encompasses a method for treating a patient with cancer (e.g. pancreatic cancer) since Chu et al. teach that various cancer

cells lines are sensitive to troxacitabine, including leukemia, lymphoma, prostate, bladder, lung, colorectal, breast, pancreas, liver, ovarian cancers (see Figure 4).

Regarding claims 3-5, Chu et al. teach that various cancer cells lines are sensitive to troxacitabine, including leukemia, lymphoma, prostate, bladder, lung, colorectal, breast, pancreas, liver, ovarian cancers (see Figure 4), which overlaps with the instant claimed limitation. Hence, one would reasonably expect to treat any suitable patient with cancer, including the various leukemia subtypes as claimed, since Chu et al. suggest that a wide variety of cancer cells are sensitive to troxacitabine and that prostate cancer cell lines, leukemia cell lines, and colon cell lines show extreme sensitivity to troxacitabine (col. 15, lines 4-7; Figure 4) and it is routine in the art to extrapolate mice data to the clinical setting to treat humans with cancer.

Regarding claim 6, the above discussion of claim 1 is incorporated by reference. Since the dose of troxacitabine as taught by the prior art overlaps with the dose range disclosed by applicant as discussed above, one would reasonably expect that administration of the same drug in overlapping doses to the same population (solid cancer patients) via continuous infusion as encompassed by the prior art would also achieve a steady state plasma concentration of troxacitabine as claimed absent objective evidence to the contrary.

Regarding claim 7, the above discussion of claim 6 is incorporated by reference.

Regarding claim 8, the above discussion of claim 1 is incorporated by reference.

Regarding claims 9-12, the above discussion of claim 6 is incorporated by reference.

Regarding claim 13, the above discussion of claim 1 is incorporated by reference.

Regarding claim 14, De Bono et al. teach troxacitabine in a dose of from 0.12 to 1.8 mg/m2/day, which overlaps with the instant claimed limitation of "1.0 to 11.0 mg/m2/day.

Regarding claim 15, De Bono et al. teach troxacitabine in a dose of from 0.12 to 1.8 mg/m2/day, which overlaps with the dose of 0.7 to 12.5 mg/m2/day of troxacitabine disclosed by applicant (specification, page 14, lines 12-24) such that one would reasonably expect to manipulate the dose of troxacitabine in order to optimize therapeutic effects of the treatment, including arriving at the instant claimed dose range, depending on the desired therapeutic outcome and patient factors such as age, weight, cancer type and severity, and tolerability since it is routine in the medical art to individualize treatment by varying the dose of drugs based on the desired therapeutic outcome and patient factors such as age, weight, tolerability, and the specific condition to be treated.

Regarding claims 17-19, the above discussion of claims 3-5 is incorporated by reference.

Regarding claims 20-22, the above discussion of claim 15 is incorporated by reference.

Regarding claim 23, De Bono et al. teach continuous infusions for five days, which overlaps with the instant claimed limitation of "administered for a period of 3 to 7 days."

Regarding claims 24-28, the above discussion of claim 23 is incorporated by reference. Since the administration period as taught by De Bono et al. overlaps with the administration disclosed by applicant, one would reasonably expect to manipulate the administration period, including arriving at applicant's claimed administration periods, in order to optimize the therapeutic effects of the treatment and minimize troxacitabine-induced toxicity depending on patient factors such as tolerability, cancer type and severity of cancer.

Regarding claims 29-32, the above discussions of claim 13 is incorporated by reference. Further, the above discussion of claim 23 is incorporated by reference. Since the administration period as taught by De Bono et al. overlaps with the administration disclosed by applicant, one would reasonably expect to manipulate the administration period and dosage amount, including arriving at applicant's claimed administration periods and dosage amount, in order to optimize the therapeutic effects of the treatment and minimize troxacitabine-induced toxicity depending on patient factors such as tolerability, cancer type and severity of cancer.

Regarding claims 33-34, De Bono et al. teach treatment intervals of every three to four weeks (abstract), which overlaps with the instant claimed limitations of "every 4 weeks" and "every 3 weeks."

Regarding claim 35, the above discussion of claims 33-34 is incorporated by reference. Further, De Bono suggest that less frequent schedules are warranted such that one would reasonably expect to manipulate the treatment interval, including arriving at applicant's claimed treatment interval, in order to optimize the therapeutic effects of

the treatment (abstract). Besides, Lokich et al. teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3), which overlaps with the instant claimed limitation of "an interval of every 5 weeks."

Regarding claim 36, the above discussion of claim 1 is incorporated by reference. Lokich et al. teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3).

Regarding claim 37, Chu et al. suggest that alkylating agents (e.g. nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin); antimetabolites; nucleoside derivatives (e.g. 5-fluorouracil); nucleoside analog of dexocytidine (e.g. cytosine arabinoside); cytidine analog (e.g. 5-azacytidine); 2-fluoroadenoside-5'-phosphate (Fludarabine); **anthracyclines**; hormonal agents ; natural products and their derivatives; 2-chlorodeoxyadenosine can be used in combination with troxacitabine to treat cancer (col. 2, line 7 to col. 3, line 10), which overlaps with the instant claimed therapeutic agents (e.g. chemotherapeutic agents).

Regarding claim 38, the above discussion of claim 37 is incorporated by reference.

Regarding claim 48, the above discussion of claim 3 is incorporated by reference.

Regarding claim 49, the above discussion of claim 5 is incorporated by reference.

Regarding claim 50, the above discussion of claim 5 is incorporated by reference.

Regarding claim 51, the above discussion of claim 36 is incorporated by reference.

Regarding claim 52, the above discussion of claim 37 is incorporated by reference.

Regarding claim 53, the above discussion of claim 38 is incorporated by reference.

Regarding claim 54, the above discussion of claim 3 is incorporated by reference.

Regarding claim 55, the above discussion of claim 36 is incorporated by reference.

Regarding claim 56, the above discussion of claim 37 is incorporated by reference.

Regarding claim 57, the above discussion of claim 38 is incorporated by reference.

Regarding claim 59, the above discussions of claim 47 is incorporated by reference. Further, Chu et al. suggest that alkylating agents (e.g. nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin); antimetabolites; nucleoside derivatives (e.g. 5-fluorouracil); nucleoside analog of dexocytidine (e.g. cytosine

arabinoside); cytidine analog (e.g. 5-azacytidine); 2-fluoroadenoside-5'-phosphate (Fludarabine); **anthracyclines**; hormonal agents ; natural products and their derivatives; 2-chlorodeoxyadenosine can be used in combination with troxacitabine to treat cancer (col. 2, line 7 to col. 3, line 10), which overlaps with the instant claimed therapeutic agents (e.g. chemotherapeutic agents).

Regarding claim 60, the above discussion of claim 59 is incorporated by reference.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Thus, it would have been obvious to a person of skill in art to at the time the invention was made to create the instant claimed invention with reasonable predictability.

Claim 39 is rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Lokich et al. (Lokich et a. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record), in further view of Chu et al. (US Patent 5,817,667) and Boote et al. (Boote et al. Phase I study of etoposide with SDZ PSC 833 as a modulator of multidrug resistance in patients with cancer. Journal of Clinical Oncology. 1996;14:610-618; abstract only).

The above discussions of De Bono et al., Lokich et al., and Chu et al. is incorporated by reference. These references do not teach PSC 833.

Boote et al. teach that PSC 833 can be administered in combination with etoposide with acceptable toxicity (abstract). Boote et al. further state that PSC 833 enhance the exposure of etoposide to cancer cells, which permit a reduction in the dose of etoposide (abstract).

It would have been obvious to a person of skill in the art at the time the invention was made to add PSC 833 as taught by Boote et al. to troxacitabine as taught by De Bono et al. to treat a patient with cancer. One would have been motivated to do so because Boote et al. suggest that PSC 833 can be administered in combination with antineoplastic drugs to treat patients with cancer and troxacitabine as taught by De Bono et al. and Chu et al. is an antineoplastic drug. Besides, Chu et al. suggest that troxacitabine may be administered in combination with other antineoplastic agents and therefore one would reasonably expect to successfully combine the PSC 833 and troxacitabine to treat a patient with cancer absent objective evidence to the contrary.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Claims 40-42 are rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Lokich et al. (Lokich et a. Dose intensity for bolus versus infusion chemotherapy

administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record), in further view of Chu et al. (US Patent 5,817,667) and Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Ed. (1996), pages 1225-1229, already made of record).

The above discussions of De Bono et al., Lokich et al., and Chu et al. are incorporated by reference. However, these references do not teach biologic response modifiers.

Goodman et al. teach biologic response modifiers (e.g. interferon alfa; page 1229). Goodman et al. teach interferon alfa as useful for treating, for example, melanoma (page 1229).

It would have bee obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references by adding a biologic response modifier (e.g. interferon alfa) to troxacitabine as taught by De Bono et al. for additive effects (e.g. against melanoma). One would have been motivated to do so because Chu et al. suggest that troxacitabine can be combined with other chemotherapy drugs and biologic response modifiers (e.g. interferon alfa) as taught by Goodman & Gilman are also chemotherapy drugs. Hence, one would reasonably expect to successfully treat a patient with said combination since De Bono disclose that troxacitabine as useful in treating melanoma and Goodman & Gilman also teach that interferon alfa is useful for treating melanoma.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Claims 43-46 are rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Lokich et al. (Lokich et a. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record), in further view of Chu et al. (US Patent 5,817,667) and Schwartz et al. (US Patent 6,444,638).

The above discussions of De Bono et al., Lokich et al., and Chu et al. are incorporated by reference. However, these references do not expressly teach sequentially or simultaneously administered chemotherapy.

Schwartz et al. (US Patent 6,444,638) teach methods of treating a patient with cancer (e.g. melanoma, lung cancer, leukemia or lymphoma) comprising administering a combination of antitumor therapeutic agents to said patient, wherein said agents may be administered sequentially or concomitantly (col. 2, line 56 to col. 3, line 31; and col. 6, line 52 to col. 7, line 7; especially col. 7, lines 52-59). Schwartz et al. state that initial drug dosage in Phase I clinical trials is usually predicated on known pharmacologic data on each drug, prior clinical experience using each drug individually (if available) and the biochemical rational for combining the drugs, and whenever possible, basic laboratory data will be used to determine sequence, schedule, modes of administration, target plasma levels, etc. (col. 28, lines 51-57). Also, Schwartz et al. teach combination

chemotherapy comprising the sequential administration of intravenous flavopiridol over 24 hours in combination with intravenous paclitaxel administered as a 24-hour infusion (col. 66, lines 36-48).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references to manipulate the sequence of administration of the individual drug components encompassed by the prior art, including arriving at applicant's claimed administration frequency, in view of the teaching of Schwartz et al., in order to optimize the therapeutic effects of the combination regimen and minimize toxicity. One would have been motivated to do so because Schwartz et al. suggest that the agents employed in combination antitumor regimens can be administered sequentially or concomitantly for treating patients with cancer (.e.g. melanoma and lung cancer; col. 2, line 56 to col. 3, line 31; and col. 6, line 52 to col. 7, line 7; especially col. 7, lines 52-59) depending on the particular drugs employed and patient factors (col. 28, lines 51-57) and Chu et al. also teach combination chemotherapy regimens for treating cancer (e.g. lung cancer (col. 2, line 7 to col. 3, line 10; and col. 15, lines 4-7; Figure 4). Besides, De Bono et al., Lokich et al. and Schwartz et al. are all concerned with infusional chemotherapy.

Regarding claim 43, Schwartz et al. teach combination chemotherapy wherein the individual drug agents may be administered sequentially or concomitantly (col. 7, lines 52-59). Besides, it is the examiner's position that it is within the skill and knowledge of an artisan skilled in the art to manipulate the order of administration of drugs absent objective evidence to the contrary.

Regarding claim 44, the above discussion of claim 43 is incorporated by reference. Hence, one would reasonably expect to administer troxacitabine in any suitable sequence when administered in combination with another chemotherapeutic agent, including simultaneously, absent objective evidence to the contrary.

Regarding claim 45, it is the examiner's position that it would have been within the skill and knowledge of an artisan skilled in the art at the time the invention was made to combine a second chemotherapeutic drug with troxacitabine and administer as separate formulation depending of the compatibility of the drugs and the sequence of administration.

Regarding claim 46, it is the examiner's position that it would have been within the skill and knowledge of an artisan skilled in the art at the time the invention was made to combine a second chemotherapeutic drug with troxacitabine and administer in combined formulation depending of the compatibility of the drugs and the sequence of administration.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Response to applicant's arguments

In response to applicant's argument that one of ordinary skill would not expect to administer a nucleoside analogue (e.g. troxacitabine) by infusion since Lokich et al. teach Ara-C (= a nucleoside analogue) has a dramatically higher MTD for bolus administration is not found to be persuasive because De Bono et al. disclose that

severe toxicity was associated with the bolus infusion and therefore one would reasonably expect to increase the duration of infusion, which would necessarily reduce the peak concentration of the drug., and reduce the toxicity associated with the shorter 30-minute infusion. Further, Lokich et al. suggest that the selection of the infusion duration of chemotherapy drugs is usually empirically selected and then later manipulated to optimize the antitumor effect of the drug and to minimize drug-induced adverse effects and that longer duration of infusions permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction (page 23, col. 1, lines 8-18). Hence, one would not reasonably consider the teaching of Lokich et al. as teaching away from continuous infusions since this reference suggest the need to manipulate the infusion rate to optimize the therapeutic effects of chemotherapy drugs. Since one of the primary goals for employing continuous infusions as disclosed by Lokich et al. is to minimize the toxicity associated with the high peak drug concentration of bolus infusions and De Bono et al. disclose severe toxicity associated with the use of bolus infusions of troxacitabine (page 15, col. 1, introduction section, lines 8-15, one would reasonably expect to successfully modify infusion duration of the bolus infusion of De Bono et al. in view of the teaching of Lokich et al. to arrive at the instant claimed invention absent objective evidence to the contrary. Besides, the teaching of Lokich et al. is supported by the teaching of Schwartz et al. that the initial drug dosage in Phase I clinical trials is usually predicated on known pharmacologic data on each drug, prior clinical experience using each drug individually (if available) and the biochemical rational for combining the drugs, and whenever possible, basic laboratory data will be

used to determine sequence, schedule, modes of administration, target plasma levels, etc. (col. 28, lines 51-57) and De Bono et al. also involves a phase I study such that one would reasonably expect to successfully modify the duration of the infusion of troxacitabine in order to reduce the toxicity observed with the bolus. Furthermore, the duration of infusion is a result-effective variable as evidenced by the teaching of Lokich et al. (page 15, col. 2, lines 3-10) and therefore one would reasonably expect to modify the infusion duration of the chemotherapy agents encompassed by the prior absent objective evidence to the contrary (MPEP 2144.05).

In response to applicant's argument that Chu et al. do not teach continuous Infusions, it is noted that Lokich et al. teach continuous infusion and therefore the combination of the cited art reasonably encompass continuous infusions. This, applicant's individualized criticism of Chu et al. is not found to be persuasive since the combination of cited references teach every claimed limitation.

Applicant's statement regarding Benet et al. is noted. However, Benet et al. was listed under "Prior Art of Record," and was not relied upon In the rejection of record.

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-15, 17-38, 43-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the following: claims 1-3, 9-10, 14-24, 30-36 of US Patent 6,630,480, in view of De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in further view of Lokich et a. Dose intensity for bolus versus infusion chemotherapy

administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record), and Chu et al. (US Patent 5,817,667).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants of each other for essentially the same reasons stated above.

In particular, reference claim 1 is directed to a method for treating acute myelogenous leukemia or chronic myelogenous leukemia in a patient comprising a compound, including the identical instantly claimed compound and the instant claims are also directed to treating patients with leukemia. It is also noted that the dosage amount recited in reference claim 33 overlaps with the claimed dosage amount recited in instant claim 14.

Unlike the instant claims, the reference claims do not claim the instant claimed continuous infusion, period of continuous infusion, or the steady state plasma levels.

The above discussions of De Bono et al, Lokich et al, and Chi et al. are incorporated by reference.

However, it would have been obvious to a person of skill in art to modify the reference method to arrive at the instant claimed invention in order to minimize the side effects of troxacitabine. One would have been motivated to do so because De Beno et al. disclose that bolus infusion of troxacitabine is associated with severe neutropenia and Chu et al. also teach methods of treatment comprising troxacitabine, while Lokich et al. is concerned with infusional anti-cancer drugs. Thus, the reference claims are deemed to be obvious variants of the instant claims for the above reasons.

Claim 39 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 9-10, 14-24, 30-36 of US Patent 6,630,480, in view of De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in further view of Lokich et a. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record), Chu et al. (US Patent 5,817,667), and Boote et al. (Boote et al. Phase I study of etoposide with SDZ PSC 833 as a modulator of multidrug resistance in patients with cancer. Journal of Clinical Oncology. 1996;14:610-618; abstract only).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants of each other for essentially the same reasons stated above.

The discussion of the above rejection with respect to reference claims 1, 3-15, 17-38, 43-60 is incorporated by reference.

Unlike the instant claims, the reference claims do recite PSC 333.

The above discussion of Boote et al. in connection with the rejection under 103(a) is incorporated by reference.

In spite of the difference, it would have been obvious to a person of skill in the art at the time the invention was made to select any suitable chemotherapy drug and combine it with troxacitabine to treat a patient with cancer. One would have been

motivated to do so because it is routine in the art to combine conventionally known chemotherapy drugs to treat cancer.

Claims 40-42 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the following: claims 1-3, 9-10, 14-24, 30-36 of US Patent 6,630,480, in view of De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in further view of Lokich et a. Dose intensity for bolus versus infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents. Ann Oncol. 1997;8(1):15-25; already made of record), and Chu et al. (US Patent 5,817,667) and Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Ed. (1996), pages 1225-1229, already made of record).

The above discussion of claims 1, 3-15, 17-38, 43-60 is incorporated by reference.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants of each other for essentially the same reasons stated above.

Unlike the instant claims, the reference claims are not directed to combination chemotherapy.

In spite of the difference, it would have been obvious to a person of skill in the art at the time the invention was made to select any suitable chemotherapy drug and combine it with troxacitabine to treat a patient with cancer. One would have been

motivated to do so because it is routine in the art to combine conventionally known chemotherapy drugs to treat cancer.

Response to applicant's arguments

It is noted that the provisional rejection regarding copending application 10/824,563 has been withdrawn since the abandonment of this application renders the rejection moot.

In response to applicant's argument regarding '480 patent that the reference claims require that the patient be previously treated with Ara-C, it is noted that the reference claims in view of the prior art encompass every claim limitation. Since the reference claims encompass the identical instantly claimed drug to treat the same population (leukemia) in overlapping doses, one would reasonably expect that the reference claims would also have the same effect as claimed.

It is noted that contrary to applicant's assertion, Lokich et al. is cited in rejection statement (see Office action, pages 12-13).

Contrary to applicant's assertion, it is noted that Giles (US '639) was not relied upon in the rejection of record.

Relevant Art of Record

The post-dated cited art made of record and relied upon is considered pertinent to applicant's invention.

Benet LZ et al. (Benet et al. Pharmacokinetics: The dynamics of drug absorption, distribution, and elimination. In, Goodman & Gilmans: The Pharmacological Basis of Therapeutics, 9th edition (1996): page 18) teach that Clinical Pharmacokinetics

attempts to provide both a more quantitative relationship between dose and effect and the framework with which to interpret measurements of concentration of drugs in biological fluids (page 18, column 1, lines 2-6). Benet LZ et al. further teach that the various physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so as a result of modification of pharmacokinetic parameters and that the three most important parameters are clearance, volume of distribution, and bioavailability; of lesser importance are the rates of availability and distribution of the agent (page 18, column 1, lines 10-19).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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16 May 2009
/C. R./
Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/
Supervisory Patent Examiner, Art Unit 1611